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Note

A convenient synthesis of 3-deoxy-3-iodo-D-glucose

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3-Deoxy-3-iodo-D-glucose (**1**), having potential utility as an X-ray contrast agent[1], has been prepared from D-allose derivatives, namely, through reaction of 1,2;5,6-di-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-allofuranose with lithium iodide[2], 1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose with either triphenylphosphite–methyl iodide[3] or triphenylphosphine–diethyl azodicarboxylate-methyl iodide[4], or methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside with methylmagnesium iodide[5]. The last method is not suitable as an industrial procedure. The others require 1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose, which has been prepared from 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose through oxidation and subsequent reduction. Oxidation[6] by ruthenium tetraoxide is, however, very expensive, and oxidation by either dimethyl sulfoxide[7,8] or pyridinium chlorochromate[9] has the disposal problem of the waste material. A direct method for the preparation of **1** from a D-glucofuranose derivative has also been reported, namely by treatment of 1,2;5,6-di-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-glucofuranose with anhydrous hydrazine, followed by treatment with iodine in the presence of *N*-methylmorpholine[10]. This method is again not appropriate, because anhydrous hydrazine often causes explosions.

In this paper, we report a more convenient, satisfactory method for the preparation of **1** from 3-*O*-*p*-tolylsulfonyl-D-glucopyranose derivatives with sodium iodide.

1,2,4,6-Tetra-*O*-acetyl-3-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (**3a**)† was treated with sodium iodide in *N*,*N*-dimethylformamide for 24 h at 130° to give two products. The major product was identical (n.m.r.) to an authentic sample of 1,2,4,6-tetra-*O*-acetyl-3-deoxy-2-iodo-β-D-glucopyranose (**5a**). From the coupling constants ($J_{2,3}$

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†The starting materials **3a** and **3b** were prepared by acetylation or benzoylation, respectively, of **2**. Compound **2** was first obtained as crystals [m.p. 124–145°, $[\alpha]_D^{22}$ +31° (*c* 1, ethanol)] when 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-glucofuranose was treated with 85% aqueous trifluoroacetic acid and the product kept in 1:10 (v/v) ethyl acetate–ethyl ether.

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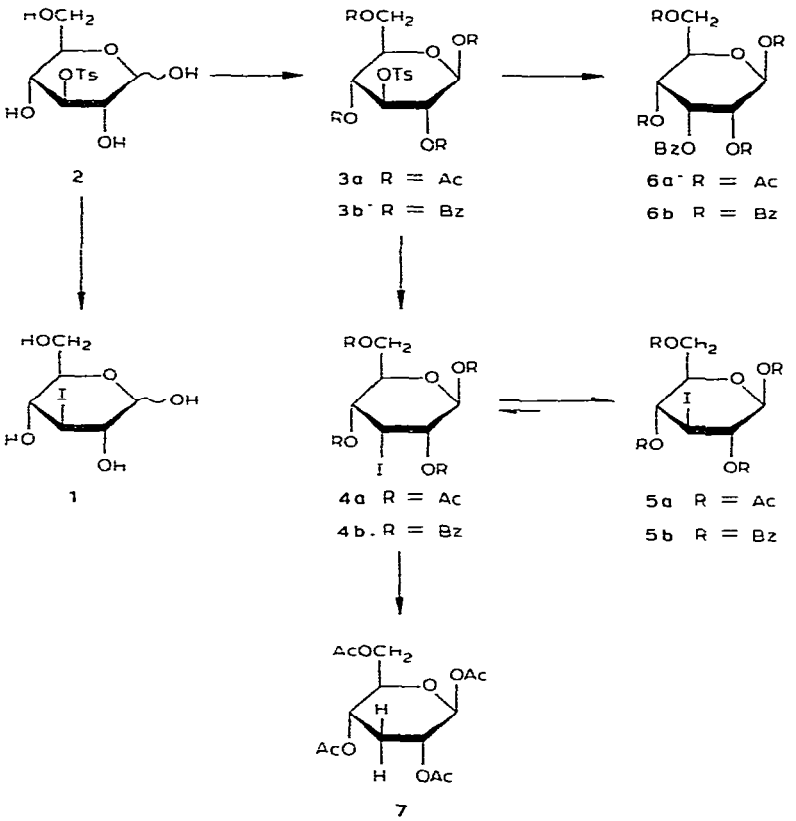

TABLE I

N.M.R. DATA

Compound	*Chemical shifts (δ) ($CDCl_3$–Me_4Si)*				*Coupling constants (Hz)*			
	H-1	*H-2*	*H-3*	*H-4*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
4a[a]	6.35 d	4.44 dd	5.29 t	4.28 dd	8	4	4	6
5a	5.63 d	5.29 dd	4.80 t	5 28 dd	8	11	11	9
4b	6 57 d	5.02 dd	5.45 t	4.88 dd	8	4	4	9.5
5b	6.13 d	5.88 dd	4.60 t	5.79 t	8	11	11	11
6a	6.16 d	5.15 dd	5.98 t	5.15 dd	8	3	3	7
6b	6.68 d	5.78 dd	6.37 t	5.70 dd	8	3	3	10

[a]Measured in benzene-d_6.

4 and $J_{3,4}$ 6 Hz), the minor product appeared to have the *allo* configuration, although the possibility of a 4-iodo derivative having the *gulo* configuration, generated through participation of the acetyl group at O-4, was not excluded. Reduction of the minor product with Raney nickel provided the 3-deoxy derivative 7. Furthermore,

1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-iodo-β-D-allopyranose (**4a**), prepared by the treatment of 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose with imidazole–triphenylphosphine–iodine[11], followed by hydrolysis and acetylation, was identical (t.l.c. and n.m.r.) to the minor product. The observed ratio of **5a** to **4a** was ~4:1, by using either *N*,*N*-dimethylformamide or dimethyl sulfoxide as solvent and various ratios of sodium iodide to **3a**, and under different concentrations

Similar results were obtained in the reaction of 1,2,4,6-tetra-*O*-benzoyl-3-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (**3b**)* with sodium iodide, which gave a ~4:1 mixture of the *gluco* (**5b**) and *allo* (**4b**) isomers.

These reactions seem to involve a substitution reaction of the *p*-tolylsulfonyl group with the iodo anion to form the 3-iodo-allopyranose derivative as the initial product, which is partially converted into the thermodynamically more stable *gluco* isomer, because the iodo group is an excellent leaving-group. In fact, only the *allo* isomer (**4a**) was detected in t.l.c. at the initial stage (after 10 min). When the reaction was monitored by t.l.c., the *gluco* isomer (**5a**) increased with time until the ratio of **5a** to **4a** became ~4:1. This is the equilibrium mixture, because ~4:1 mixtures of **5a** and **4a** were obtained by the reaction of pure **4a** and **5a**, respectively. Even in the absence of sodium iodide, equilibration readily occurred on heating at 130° in *N*,*N*-dimethylformamide in the case of the benzoates **4b** and **5b** (2 h); however, a longer time (~20 h) was required for the acetates **4a** and **5a**.

Hughes and Speakman[12] prepared 1,2,3,4,6-penta-*O*-benzoyl-β-D-allopyranose (**6b**) by the reaction of **3b** with sodium benzoate. We have performed the same reaction, as well as a similar reaction of the acetate **3a** with sodium benzoate, and have obtained only the corresponding 3-*O*-benzoyl derivatives having the *allo* configuration (**6a**,**b**). This result is reasonable, because the benzoyloxy group is a less effective leaving-group than the iodo group.

When the α anomer of the acetate **3a** was treated similarly with sodium iodide or sodium benzoate, the starting material was recovered in good yield. These results are explicable in terms of steric hindrance between an approaching nucleophile and the acyloxy group at the anomeric position.

Similar treatment of the unprotected 3-*O*-*p*-tolylsulfonyl-D-glucose (**2**)* afforded the desired 3-deoxy-3-iodo-D-glucose (**1**) in 45% yield. By use of this method, compound **1** could be readily prepared, even on a large scale, from D-glucose in only four steps (overall yield 30%), namely, isopropylidenation, tosylation, hydrolysis, and iodination, without use of expensive reagents

EXPERIMENTAL

General methods. — Melting points are uncorrected. Specific rotations were determined with an ERMA polarimeter. N.m.r. spectra were recorded at 100 MHz with a JNM-PS-100 (JEOL) spectrometer, with tetramethylsilane as the internal

*See footnote † on p. 121.

standard. High-performance liquid chromatography (l.c.) was performed with a Hitachi 635A instrument with Lichrosorb RP-18. Thin-layer chromatography was performed with Silica Gel 5715 (Merck, Darmstadt). Column chromatography was conducted on Silica Gel C-300, (Wako gel, Japan). Solutions were evaporated under diminished pressure.

*1,2,4,6-Tetra-*O*-acetyl-3-deoxy-3-iodo-β-*D*-gluco-* (**5a**) *and -allo-pyranose* (**4a**). — A solution of 1,2,4,6-tetra-*O*-acetyl-3-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (**3a**) (7 g, 13.9 mmol) and sodium iodide (6.3 g, 42 mmol) in *N*,*N*-dimethylformamide (28 mL) was heated for 24 h at 130° with stirring. The mixture was cooled and then evaporated. The residue was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with a 1% solution of sodium thiosulfate and then water, dried, and evaporated. The residue was crystallized from 2-propanol (10 mL) to yield 3.5 g of **5a**. The syrup (2 g) obtained by evaporation of the mother liquor was similarly treated with sodium iodide (1.7 g) as just described to afford an additional amount of **5a** (1.1 g); total yield, 72%; m.p. 118–119°, $[\alpha]_D^{22}$ +20° (*c* 1, chloroform).

Anal. Calc. for $C_{14}H_{19}IO_9$: C, 36.69; H, 4.18. Found: C, 36.49; H, 4.07.

The remaining solutions were combined and evaporated. The residue was chromatographed on silica gel with 19:1 (v/v) isopropyl ether–benzene as eluant. The fractions having R_F 0.45 [4:1 (v/v) isopropyl ether–benzene] were collected and evaporated to give 1.1 g (16%) of **4a**, which crystallized gradually; m.p. 89–90°, $[\alpha]_D^{22}$ +4° (*c* 0.5, chloroform).

Anal. Calc. for $C_{14}H_{19}IO_9$: C, 36.69; H, 4.18. Found: C, 36.42; H, 4.15.

*1,2,4,6-Tetra-*O*-benzoyl-3-deoxy-3-iodo-β-*D*-gluco-* (**5b**) *and -allo-pyranose* (**4b**). — A solution of 1,2,4,6-tetra-*O*-benzoyl-3-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (**3b**) (7 g, 9.3 mmol) and sodium iodide (4.2 g, 28 mmol) in *N*,*N*-dimethylformamide (50 mL) was heated for 24 h at 130° with stirring. After being cooled, the mixture was filtered through a pad of Celite 545 (Johns–Manville), and the filtrate evaporated. The residue was dissolved in chloroform and washed successively with water, 1% sodium thiosulfate, and water, dried, and evaporated to a solid. The solid was washed with methanol (5 mL) and then recrystallized from chloroform–methanol to afford 3.95 g (60%) of **5b**; m.p. 238–239°, $[\alpha]_D^{22}$ +18° (*c* 1, chloroform).

Anal. Calc. for $C_{34}H_{27}IO_9$: C, 57.80; H, 3.85. Found: C, 57.90; H, 3.99.

The mother liquor was evaporated and chromatographed on silica gel with chloroform as eluant. The fractions having R_F 0.72 [4:1 (v/v) isopropyl ether–hexane] were collected and evaporated to give 0.98 g (14.8%) of **4b**, which crystallized from chloroform–methanol; m.p. 178–180°, $[\alpha]_D^{22}$ +20° (*c* 1, chloroform).

Anal. Calc. for $C_{34}H_{27}IO_9$: C, 57.80; H, 3.85. Found: C, 57.84; H, 3.80.

*1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzoyl-β-*D*-allopyranose* (**6a**). — A solution of **3a** (2 g, 3.98 mmol) and anhydrous sodium benzoate (3 g, 20.8 mmol) in *N*,*N*-dimethylformamide (60 mL) was heated for 18 h at 130° with stirring. The mixture was cooled and then filtered through a pad of Celite 545 (Johns–Manville), and the filtrate was

evaporated. The syrup was chromatographed on silica gel eluted with benzene, to afford **6a** as a syrup in 60% yield (1.1 g); $[\alpha]_D^{22}$ −30° (*c* 1, chloroform).

Anal. Calc. for $C_{21}H_{24}O_{11}$: C, 55.75; H, 5.35. Found: C, 55.51; H, 5 37.

3-Deoxy-3-iodo-D-*glucose* (**1**). — A solution of 3-*O*-*p*-tolylsulfonyl-D-glucose (**2**; 2 g, 6 mmol) and sodium iodide (2.7 g, 18 mmol) in *N*,*N*-dimethylformamide (20 mL) was heated for 4 h at 120° with stirring. The mixture was cooled and evaporated. The residue was dissolved in water and the solution passed through a column of Amberlite 200C (H^+; 200 mL) plus Diaion WA-20 (free-base; 200 mL). U.v. (255 nm)-active fractions were collected and evaporated to a syrup that crystallized from ethanol to yield 0.98 g (45%) of **1**, m.p. 142–143° (lit.[2] m.p. 140–142°), $[\alpha]_D^{22}$ +58.2° (*c* 2.5, water).

Anal. Calc. for $C_6H_{11}IO_5$: C, 24.84; H, 3.83. Found: C, 24.73; H, 3.80.

Acetylation of **1** with acetic anhydride–pyridine afforded **5a** and its α anomer.

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